Blending of agglomerates into powders

Willemsz, Tofan Abraham

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Summary

Dry blending of powders is an extremely important unit operation in the (pharmaceutical) industry. Frequently, active pharmaceutical ingredients (or other compounds like dies) consist of particles which are cohesive. These particles have the tendency to form agglomerates. Presence of agglomerates of a drug in blend poses a potentially serious safety risk because individual dosage forms contain very high doses of drug. This demonstrates that blend homogeneity is a very important topic of attention in the pharmaceutical industry. Agglomerates need to be broken and dispersed and removal of agglomerations is therefore a critical aspect in the dry mixing processes.

The objective of this thesis is to identify the basic mechanisms of agglomerate breakage during blending of powders. This mechanism is the basis to assess the critical process parameters and provide quantitative design rules for conceptual design of the mixing process and scale up.

The purpose of **chapter 2**, is to obtain more insight in the mechanisms that lead to the break-up of assemblies of powder particles in a moving powder bed. The break-up of aggregates was studied by application of so-called brittle Calibrated Test Particles (*bCTPs*). Tests using *bCTPs* provided evidence that agglomerates reduce in size via an abrasion mechanism. This made it possible to introduce a mechanistic description to quantify the abrasion rates of agglomerates during a dry powder blending. The study showed that the rate of abrasion is not only influenced by the (mechanical) properties of the agglomerates and process conditions such as mixing intensity, but also by the particle size distribution of the bulk filler.

From the study in **chapter 2**, it became clear that there are hence a large number of parameters that potentially affect the abrasion behavior of agglomerates and therefore the final result of the blending process. Results in **chapter 2** indicate that the speed at which particles move in a mixer is a crucial parameter. Traditionally, the method to measure particle velocity is particle image velocimetry. Often this method requires presence of tracer materials to enhance contrast. This method of contrast enhancement is often not acceptable in an industrial setting, while test at large scale were considered necessary to achieve the purpose of this thesis.

Therefore in **chapter 3**, the development of the novel method to measure powder velocities on the surface of the dry powder bed is described and called “powder surface velocimetry” (PSV). PSV is a method based on mapping the movement of small structures

called fingerprints. Identification of these structures is based on a statistical correlation function. The method is able to identify structures to assess the velocity of a powder under conditions of low contrast, i.e. a powder bed. Importantly, addition of tracer particles is not necessary, which is needed when the tests need to be performed in a large scale industrial setting.

Powder surface velocimetry results made it possible to develop a model based on the mechanistic understanding from **chapter 2**, **chapter 4** describes the approach to quantitatively model the relationships between powder motion during blending and agglomerate abrasion. For this purpose the kinetic energy density of the bed is related to the work of fracture of agglomerates. The ratio of these numbers is a Stokes number referred to as the Stokes abrasion number (St_{Abr}) in this thesis. The conclusion is that particle velocity critically affects agglomerate abrasion and with that mixing time.

In **chapter 5**, the St_{Abr} number approach to support scale-up and technology transfer of a mixing process is discussed. The impacts of a number of process parameters have been studied. Application of St_{Abr} numbers gives the possibility to assess how the agglomerate abrasion rate scales with process variables in different types/scale of high-shear mixers, because it appears that St_{Abr} alone explains around 80% of the total variance. The St_{Abr} approach demonstrates to be a useful tool to predict the abrasion of agglomerates during blending when technology is transferred between mixer scales/types. In addition, applying the St_{Abr} approach revealed a transition point between parameters that determined agglomerate abrasion. At low fill volumes the moving impeller in the mixer occupies a relatively large fraction of the powder volume. This increases the chances of direct impact of impeller blades with agglomerates. This makes that the St_{Abr} approach has less predictive power.

The tumbling blender is currently one of the most common mixers used in the pharmaceutical industry. Normally the device has no mechanical agitators (e.g. intensifiers) to break-up agglomerates leading to undesired excessively long mixing times or to blend in-homogeneity. Only limited studies have been reported on the influence of blending conditions on agglomerate abrasion in tumbling blenders.

In **chapter 6**, the Stokes number approach has been used to describe the quantitative characterization of agglomerate abrasion in a tumbling blender. In this study the St_{Abr} approach revealed a transition-point between abrasion rate behaviors which is determined by the fill level of the blender. Below this transition point a blending condition exist where agglomerate abrasion is dominated by the kinetic energy density of the powder blend.

Above this transition point, a blending condition exists where agglomerates show (undesirably) slow abrasion rates.